**Prevalence of Microcephaly in Europe : A Population based study**

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**Prevalence of Microcephaly in Europe**

Abstract

Objectives

Microcephaly is a congenital anomaly where the baby’s head is smaller than expected when compared with babies of the same sex, age and ethnicity. Many of these babies will have underdeveloped brains. This study aimed to provide contemporary estimates of the prevalence of microcephaly in Europe, determine if the diagnosis of microcephaly is consistent across Europe and to evaluate whether changes in prevalence would be detected using the current European surveillance performed by EUROCAT (the European Surveillance of Congenital Anomalies).

Design

A questionnaire and a population-based, observational study

Setting

24 EUROCAT registries covering 570,000 births annually in 15 countries.

Participants

2443 cases of microcephaly not associated with a genetic condition, among live births, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly at any gestation.

Main Outcome Measures

Prevalence of microcephaly (1st Jan 2003- 31st Dec 2012) analysed using random effects Poisson regression models to account for heterogeneity across registries.

Results

Sixteen registries responded to the questionnaire of whom 44% (7/16) used the EUROCAT definition of microcephaly (a reduction in the size of the brain with a skull circumference more than 3 standard deviations (SD) below the mean for sex, age and ethnic origin), 19% (3/16) used a 2 SD cut-off, 31% (5/16) were reliant on the criteria used by individual clinicians and one registry changed criteria between 2003 and 2012.

Prevalence of microcephaly in Europe was 1.53 (95% CI : 1.16-1.96) per 10,000 births with registries varying from 0.4 (95% CI : 0.2-0.7) to 4.3 (95% CI : 3.8-4.8) per 10,000 (Chi-squared =338 with 23 degrees of freedom, I2 = 93%). Registries with the 3 SD cut-off reported a prevalence of 1.74 per 10,000 (95% CI: 0.86-2.93) compared with those with the less stringent 2 SD cut-off of 1.21 per 10,000 (95% CI: 0.21-2.93).

The prevalence of microcephaly would need to increase in 1 year by over 35% in Europe or by over 300% in a single registry to reach statistical significance (p<0.01).

Conclusions

EUROCAT could detect increases in the prevalence of microcephaly due to the Zika virus of a similar magnitude to those observed in Brazil. However, due to the rarity of microcephaly and discrepant diagnostic criteria, the smaller increases expected in Europe would be unlikely to be detected. Clear diagnostic criteria for microcephaly must be adopted across Europe.

**What this paper adds**

**What is already known on this subject**

* Zika virus infection during the first trimester of pregnancy increases the risk of microcephaly in the baby.
* In South America clinicians noticed a dramatic increase in the prevalence of microcephaly, which was confirmed by congenital anomaly registries.
* European surveillance of congenital anomalies is performed by EUROCAT (the European Surveillance of Congenital Anomalies; <http://www.eurocat-network.eu/>).

**What this study adds**

* The reported prevalence of microcephaly across Europe varies considerably, due to the different diagnostic criteria applied and varying levels of ascertainment.
* EUROCAT could detect increases in the prevalence of microcephaly due to the Zika virus of a similar magnitude to those observed in Brazil.
* Smaller increases in the prevalence of microcephaly , due to the *Aedes* mosquitos not being indigenous in Europe. would be unlikely to be detected.

**Introduction**

Microcephaly is a congenital anomaly where a baby’s head is smaller compared with other babies of the same sex, age and ethnicity. The definition of “smaller “ varies from a head circumference more than 2 standard deviations (SD) below the mean to more than 3 SDs below the mean. The more extreme the definition of “smaller” the greater the proportion of babies diagnosed with microcephaly who will have smaller underdeveloped brains and who are consequently at risk of developmental delay, intellectual disability and physical disabilities such as hearing and vision impairment.[1] In a cohort of 680 children with microcephaly the aetiology of 31% was genetic, 27% perinatal brain injuries (including 4% maternal exposure to teratogens), 2% postnatal brain injuries, and 41% unknown.[2]

In late 2015, there were reports of a dramatic increase in the prevalence of microcephaly in Brazil coinciding with an outbreak of the Zika virus several months earlier. [3] There is now sufficient evidence to confirm that Zika virus infection during the first trimester of pregnancy increases the risk of microcephaly in the baby. [4,5] The emerging microcephaly epidemic across South America has highlighted the necessity of accurate congenital anomaly surveillance. This study aimed to provide contemporary estimates of the prevalence of microcephaly in Europe, determine if the diagnosis of microcephaly is consistent across Europe and to evaluate whether changes in prevalence would be detected using the current European surveillance performed by EUROCAT (the European Surveillance of Congenital Anomalies; <http://www.eurocat-network.eu/>).

**Methods**

EUROCAT is a Europeannetworkof almost all population-based congenital anomaly registries in Europe and currently provides the most complete information on congenital anomalies occurring in Europe. EUROCAT was established in 1979 and there are currently 43 registries in 23 countries covering more than 29% of European births (1.7 million) per year. The European Union has provided funding for a central registry to coordinate the network, and the member registries are funded locally by national or regional governments, research, or other bodies. All EUROCAT registries have a defined geographical coverage (see map for registries included in EUROCAT at http://www.eurocat-network.eu/content/EUROCAT-Population-Table-I-Year2012.pdf); in some countries all births are covered by a registry (for example Hungary, Malta, Norway, Poland and Sweden) and in some countries less than 10% of that country’s birth population are covered by a registry (for example Germany, the Netherlands and Ukraine).

All EUROCAT registries use multiple sources of information to ascertain cases in live births, late fetal deaths (>20 weeks’ gestation), and terminations of pregnancy for fetal anomaly at any gestation. [6] Data sources, depending on registry, include maternity, neonatal, and paediatric records; fetal medicine, cytogenetic, pathology, and medical genetics records; specialist services including paediatric cardiology; and hospital discharge and child health records. The EUROCAT central database is hosted by the European Commission Joint Research Centre in Ispra, Italy. Registries either submit individual anonymised records of cases of congenital anomalies (full members) or submit the same data in aggregate form (associate members). All cases are coded to the International Classification of Diseases (ICD) version 9 or 10 with 1-digit British Paediatric Association (BPA) extension. Each case can have one syndrome and up to eight malformation codes. All coding is standardised by using the EUROCAT guide (version 1.4) with isolated minor anomalies, e.g. skin tags, being excluded. [7]

A set of 30 data quality indicators is used to assess five key elements of data quality: completeness of case ascertainment, accuracy of diagnosis, completeness of information on EUROCAT variables, timeliness of data transmission, and availability of population denominator information. [8] Surveillance and research are performed using data only from registries with sufficiently high data quality. For inclusion in the annual monitoring of trends registries must not be more than 1 year behind in data transmission and have provided data for at least nine of the previous ten years. [9] Twenty-five registries satisfied this criterion for 1st January 2003 to 31st December 2012.

In EUROCAT’s annual monitoring of trends for congenital anomalies excluding genetic conditions, all cases with a chromosomal anomaly, genetic syndrome, microdeletion or skeletal dysplasia are excluded for two reasons. Firstly, registries differ in their reporting of associated anomalies in cases with a genetic condition and secondly, these genetic conditions are aetiologically different from other anomalies. For example, over 10% of cases with Patau syndrome have microcephaly [10] and the risk of a pregnancy with Patau syndrome increases with maternal age. Therefore, if mean maternal age increased in a population, more cases with Patau syndrome would occur and hence more cases with microcephaly would also occur. This increase in microcephaly could mask other important trends due to changes in the exposure to teratogens. Known genetic conditions are well recorded as the majority of registries receive information directly from cytogenetic laboratories as indicated by a specific data quality indicator assessing Down syndrome ascertainment. In June 2014, the EUROCAT Central Registry extracted aggregate data on all cases of microcephaly excluding genetic conditions from 1st Jan 1980 to 31st Dec 2012.

The EUROCAT definition of microcephaly is: “a reduction in the size of the brain with a skull circumference more than 3 SDs below the mean for sex, age and ethnic origin”. [7] However, many registries receive the diagnosis of microcephaly from a clinician and may not be able to ensure that the EUROCAT definition is used. To find out whether this was the case, a questionnaire was sent to all EUROCAT registries with the following questions:

* Do you have a strict definition of microcephaly?
* Do you use the EUROCAT definition?
* Do you use growth charts for defining microcephaly?
* Do you report the cases that the clinicians report to you or do you assess the diagnosis within your registry?

A Poisson random effects model was fitted to estimate the European prevalence of microcephaly from 2003 to 2012 and the degree of heterogeneity was examined using the I2 test statistic. A Poisson model was used as these models are used to predict the number of times a rare event (in this case microcephaly) will occur when many general events occur (in this case all pregnancies). A random effects model assumes that the true prevalence of microcephaly in each registry will vary. Poisson regression models were fitted for the number of microcephaly cases diagnosed each year with the total number of births in the population each year as the exposure variable to examine linear trends in the years from 2003 to 2012 for each registry separately. Multilevel Poisson regression models were also fitted using the data from 1980 to 2012 with data from each two yearly interval combined and entered as a categorical variable and each registry as a strata in order to estimate a registry adjusted two yearly prevalence of microcephaly. Two years was chosen to reduce the random fluctuations present in the data. All analyses were performed using Stata software version 12.

*Patient involvement*

As this study is part of EUROCAT’s routine surveillance of congenital anomalies no patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for implementation of the study. No patients were asked to advise on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants. However, the results will be available on the EUROCAT website.

**Results**

Sixteen of the 25 participating registries (64%) replied to the EUROCAT microcephaly questionnaire. One registry changed their diagnostic criteria for microcephaly from below the 10th centile to below the 3rd centile in 2006 and therefore it was excluded from the data analysis. Seven (44%) registers used the 3 SD cut-off recommended by EUROCAT, three (19%) used a 2 SD cut-off and the remaining five (31%) registers were reliant on the criteria used by individual clinicians. The majority of registries used country-specific growth charts with one registry using the WHO 2006 Child Growth Standard.[11]

Table 1 shows the considerable variations in birth population surveyed by the 24 registries, with the largest registry covering almost 100,000 births per year and the smallest only 3,500. Microcephaly is a rare congenital anomaly and hence only two registries (8%) diagnosed on average more than 10 cases a year and 15 registries (63%) had at least one year from 2003 to 2012 during which they did not diagnose a single case. In total, there were 570,000 births resulting in 100 cases of microcephaly per year. Figure 1 shows the changes in the biennial prevalence of microcephaly (adjusted for registry) from 1980 to 2012. Large changes in prevalence have occurred as shown in figure 1 when, for example, the European prevalence increased by 37% from 1992 to 1994, for no identifiable reason other than chance, and decreased four years later.

The estimated prevalence of microcephaly in Europe from 2003 to 2012 was1.53 (95% CI : 1.16-1.96) per 10,000 births (figure 2). There was considerable heterogeneity between registries (Chi-squared =338 with 23 degrees of freedom, I2 = 93%). There was no indication that registries employing a more stringent diagnostic criteria had a lower prevalence compared with those with less stringent criteria : seven registries that used the 3 SD cut-off reported a prevalence of 1.74 per 10,000 (95% CI: 0.86-2.93), three registries that used a 2 SD cut-off a prevalence of 1.21 per 10,000 (95% CI: 0.21-2.93) and five registries that were reliant on the criteria used by individual clinicians a prevalence of 1.81 per 10,000 (95% CI : 0.29 – 4.57).

For the 10 years from 2003 to 2012, there was an average annual decrease in the prevalence of microcephaly of 2.2% (95% CI: -4.4% to 0.0%) per year (Table 1). There was considerable heterogeneity between registries for this trend in prevalence (Chi-squared = 79.29 with 23 degrees of freedom, I2 = 71%).

### Discussion

This study has shown that the prevalence of microcephaly across Europe varies considerably, which is likely to be due to a combination of three different factors: (i) the diagnostic criteria and how they are applied (ii) the different levels of ascertainment (registries with active ascertainment procedures show a higher prevalence than registries with more passive procedures) and (iii) the application of growth curves to populations with different ethnic backgrounds.

The prevalence of microcephaly cases reported here excluded all cases with a genetic condition (a chromosomal anomaly, genetic syndrome, microdeletion or skeletal dysplasia). In EUROCAT an additional 23% of microcephaly cases have a genetic condition. This is lower than the 31% of cases with a genetic condition observed in a study on the etiology of microcephaly in 680 children.[2] This may be due to some registries not including all associated anomalies in cases with a genetic condition.[10] Inflating the observed prevalence of microcephaly in this study by 31% gives an estimated prevalence of microcephaly including genetic conditions of 2.0 per 10,000 (1.53\*1.31). This compares with reported prevalences including genetic conditions of 0.5 per 10,000 (95% CI : 0.4 – 0.6) in Brazil (prior to the Zika virus epidemic)[12], 2.3 per 10,000 (95% CI : 1.82 – 2.78) in India [13] and 6.0 per 10,000 (95% CI : 4.5-7.7) in the USA. [14]

In this study around 100 cases of microcephaly occurred each year (table 1). As the occurrence of cases has approximately a Poisson distribution, if the numbers of births does not change significantly an increase of over 35% of cases in 1 year would be required to be identified as a statistically significant increase at p < 0.01 (100 vs 135 is p = 0.009). The average number of cases per registry per year is four (table 1) and hence the prevalence would need to increase by over 300% in a single registry to reach statistical significance (4 vs 13; p=0.006). If multiple comparisons were adjusted for, such increases would need to be greater.

In Brazil, the Live Birth Information System (Sistema de Informações sobre Nascidos Vivos [SINASC]) collects information on all congenital anomalies amongst live births and is estimated to have a coverage of > 95%. [11] During 2000–2014, on average 157.3 cases of microcephaly were registered in SINASC each year from 2.9 million live births giving a prevalence of 0.5 per 10,000. The prevalence rose to 2 per 10,000 in 2015 (574 cases, a 370% increase), with the prevalence in the North East rising to 5.6 per 10,000 (a 10-fold increase). Such increases were quickly detected and linked to the increased transmission of the Zika virus. As calculated above, the EUROCAT surveillance system would have detected increases of this magnitude. Future increases in prevalence of microcephaly in Europe due to the Zika virus would be expected to be considerably smaller than those that have occurred in South America, due to the *Aedes* mosquitos not being indigenous in Europe. Hence such changes in prevalence would be unlikely to be detected through routine surveillance. However, maternal exposure to the Zika virus should be considered for any newly diagnosed microcephaly cases.

The strength of this study is that the EUROCAT registries are population-based and cover 600,000 births annually in 15 countries. In addition, all cases are included, not just those that are receiving treatment at specialist hospitals. A limitation of EUROCAT is that the definition of a case of microcephaly is, for many registries, at the discretion of the patient’s clinician. This means that standardising diagnostic criteria can be very difficult. There are clear discrepancies in the application of the diagnostic guidelines as, if head circumference had a Gaussian (normal) distribution, we would expect the head circumference in 0.13% of babies to be more than 3 SDs below the mean and in 2.3% to be more than 2 SDs below the mean (prevalences of around 13 per 10,000 to 230 per 10,000), inconsistent with the observed prevalences from Europe, Brazil, India and the USA.[12,13,14] In the case of microcephaly, collecting additional information such as the gestation age of the baby at birth, the age of the baby at the time of diagnosis of microcephaly, the head circumference of the child and also the ethnic group of the child would enable EUROCAT to more accurately determine discrepancies in diagnosis and also to ensure more consistent diagnostic criteria.

The recent (4 March 2016) WHO interim guidelines for diagnosing microcephaly are: “Neonates with a head circumference more than 2 standard deviations below the mean are considered to have microcephaly. Neonates with a head circumference more than 3 standard deviations below the mean should be considered to have severe microcephaly.” [15] Implementation of this new definition will greatly increase the prevalence of microcephaly with potentially an additional 2.2% (2.3%-0.1%) of babies having microcephaly diagnosed. This will result in the proportion of babies labelled as microcephalic who will have no detectable neurological impairment being much greater. [1] The feasibility of such a change requires further assessment. The application of the WHO definition has other limitations in Europe. The WHO has a set of tables with head circumference for term neonates [11] and recommends the use of Intergrowth standards for preterm neonates. [16]However, studies from Norway, Belgium and the UK have found that the WHO tables are not accurate for the children in their cohorts [17,18]; these children had larger heads, which would result in the under–diagnosis of microcephaly. Similarly, these tables may not be suitable for children from other ethnic groups that have smaller heads on average.

The emergence of the Zika virus and its association with microcephaly highlights the necessity for a more standardised application of agreed diagnostic criteria of microcephaly. It also emphasises the necessity of continued surveillance of all congenital anomalies within each country in Europe. Potential teratogens are often identified by alert clinicians (such as in the case of thalidomide). Congenital anomaly registries with accurate baseline data are then essential to evaluate the true severity of any new epidemic. For rare diseases, the pooling of standardised data across Europe by EUROCAT to obtain accurate baseline data is essential in order to detect and evaluate any future environmental teratogens in a timely manner.

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All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

**Transparency declaration**

JKM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**Details of Contributors**

JKM, JR and EG conceived the study. JKM did the statistical analysis and wrote the first draft

of the article. EG wrote the questionnaire and distributed it. JR, EG, ML and HD made substantial contributions to interpretation of results and revision of the manuscript. All other co-authors were registry representatives from EUROCAT participating registries. They contributed and validated their data and participated in the interpretation of results and critical revision of manuscript. JKM is the guarantor.

**Ethics**

Local procedures regarding ethics approval for the registries’ activities and their collaborations with EUROCAT are available on the EUROCAT website (www.eurocat-network.eu/ABOUTUS/Member-Registries/ MembersAndRegistryDescriptions/AllMembers).

**Data Sharing Statement**

The data used in this study belong to the individual registries. However, requests for case data can be made to the JRC-EUROCAT Central Registry (JRC-EUROCAT@ec.europa.eu) who will ask the individual registries permission to use the data. Aggregate data, updated biannually, are available from the EUROCAT website http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. Data included in the paper was extracted from the EUROCAT database in April 2014.

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Legends to Figures

Figure 1 : European prevalence (per 10,000 births) and 95% CI of microcephaly excluding genetic conditions: 1980-2012

Figure 2: Prevalence (per 10,000 births) and 95% CI of microcephaly excluding genetic conditions according to EUROCAT registry (2003-2012) (European 95% CI in grey)

Table 1 : Number of microcephaly cases (excluding genetic conditions) according to EUROCAT registry since 1980

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Registry | 1st Year | Final Year | Number of years of data | Average number of cases per year | Average number of births per year | Number of years with no cases 2003-2012 | Number of cases per 10,000 births 2003-2012 (95% CI) | Annual change in prevalence 2003-2012 (95% CI) |
| Hungary | 1998 | 2011 | 14 | 15.3 | 96,297 | 0 | 1.8 ( 1.6 - 2.1 ) | 2% ( -4% - 8% ) |
| UK, East Midlands and South Yorkshire | 1998 | 2012 | 15 | 8.5 | 66,577 | 0 | 1.0 ( 0.8 - 1.3 ) | -6% ( -13% - 2% ) |
| Norway | 1999 | 2012 | 14 | 2.7 | 59,753 | 1 | 0.5 ( 0.3 - 0.7 ) | -2% ( -14% - 12% ) |
| UK, Wales | 1998 | 2012 | 15 | 15.8 | 33,448 | 0 | 4.3 ( 3.6 – 5.0 ) | -11% ( -16% - -6% ) |
| France, Paris | 1981 | 2012 | 32 | 8.0 | 33,044 | 0 | 2.9 ( 2.3 - 3.6 ) | 8% ( 0% - 17% ) |
| UK, Northern England | 2000 | 2012 | 13 | 4.5 | 32,056 | 1 | 1.3 ( 0.9 - 1.7 ) | -17% ( -26% - -7% ) |
| Italy, Emilia Romagna | 1981 | 2012 | 32 | 3.4 | 28,484 | 1 | 1.2 ( 0.9 - 1.6 ) | 13% ( 1% - 26% ) |
| UK, Wessex | 1994 | 2012 | 19 | 2.3 | 27,599 | 0 | 0.8 ( 0.6 - 1.2 ) | -11% ( -23% - 3% ) |
| Ireland, Dublin | 1980 | 2012 | 33 | 6.3 | 22,521 | 0 | 2.2 ( 1.7 - 2.9 ) | -18% ( -26% - -10% ) |
| Italy, Tuscany | 1980 | 2012 | 33 | 1.8 | 20,809 | 0 | 0.7 ( 0.4 – 1.0 ) | -9% ( -23% - 6% ) |
| Spain, Basque Country | 1990 | 2011 | 22 | 3.6 | 18,155 | 0 | 2.9 ( 2.2 - 3.8 ) | 11% ( 0% - 23% ) |
| Netherlands, North | 1981 | 2012 | 32 | 3.8 | 16,581 | 1 | 1.7 ( 1.2 - 2.4 ) | 16% ( 1% - 32% ) |
| Belgium, Antwerp | 1990 | 2012 | 23 | 4.0 | 15,778 | 1 | 2.3 ( 1.7 - 3.1 ) | -3% ( -13% - 7% ) |
| Portugal, South | 1990 | 2011 | 22 | 1.8 | 15,432 | 5 | 0.4 ( 0.2 - 0.8 ) | 0% ( -17% - 19% ) |
| UK, Thames Valley | 1991 | 2012 | 22 | 1.1 | 14,679 | 1 | 0.9 ( 0.6 - 1.4 ) | -1% ( -8% - 6% ) |
| France, Isle de Reunion | 2002 | 2012 | 11 | 4.6 | 14,596 | 0 | 3.2 ( 2.4 - 4.3 ) | 22% ( 9% - 36% ) |
| Belgium, Hainaut | 1980 | 2012 | 33 | 2.6 | 11,465 | 1 | 1.5 ( 1.0 - 2.3 ) | -4% ( -13% - 5% ) |
| Ireland, Cork and Kerry | 1996 | 2012 | 17 | 2.1 | 8,907 | 5 | 0.9 ( 0.5 - 1.8 ) | -3% ( -15% - 12% ) |
| Switzerland, Vaud | 1989 | 2012 | 24 | 1.5 | 7,600 | 2 | 1.7 ( 1.0 - 2.9 ) | 1% ( -12% - 16% ) |
| Ireland, South East | 1997 | 2012 | 16 | 2.1 | 6,796 | 3 | 2.3 ( 1.4 - 3.7 ) | -12% ( -26% - 4% ) |
| Croatia, Zagreb | 1983 | 2012 | 30 | 1.7 | 6,367 | 6 | 0.6 ( 0.2 - 1.5 ) | 4% ( -9% - 18% ) |
| Denmark, Odense | 1980 | 2012 | 33 | 1.0 | 5,272 | 6 | 1.0 ( 0.4 - 2.3 ) | -7% ( -20% - 9% ) |
| Malta | 1986 | 2011 | 26 | 1.2 | 4,619 | 1 | 3.0 ( 1.7 - 5.4 ) | 3% ( -9% - 17% ) |
| Germany, Mainz | 1990 | 2011 | 22 | 0.4 | 3,425 | 6 | 1.4 ( 0.5 - 3.6 ) | 1% ( -15% - 21% ) |
| European Estimate |  |  |  | 100.1 | 570,260 |  | 1.53 (1.16 – 1.96) | -2% ( -4% - 0% ) |